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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/244,130	02/04/99	DUJON B	3495.0111-10

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FINNEGAN HENDERSON FARABOW
GARRETT AND DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

EXAMINER	
KAUSHAL,S	
ART UNIT	**PAPER NUMBER**
1633	5

DATE MAILED: 10/26/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/244,130	DUJON et al
Examiner	**Group Art Unit**
SUMESH KAUSHAL	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 23-47 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 23-47 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

The instant application is DIV of 09/119,024 filed 07/20/98 now patent 5,948,678, which is CON of 08/336,241 filed 11/07/94 now patent 5,792,632, which is CIP of 07/911,160 filed 11/05/92 now patent 5,474,896, which is CIP of 07/879,689 filed 05/05/92 now abandoned.

Preliminary amendment filed in Paper No. 4 filed 6/10/99 is entered claim 1-22 are canceled and newly filed claims 23-47 are examined in this office action.

The instant application contains typographical errors (see page 48, line 2, word: Polybrain). The applicant is advised to review the application for other typographical mistakes. An explanation of any correction is required.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23-24, 27, 28, 31-32 and 39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15, 18, 21, 28 of copending Application No.08/643732. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 15 and 28 of 08/643,732 are drawn to a non-human transgenic animal comprising a cell comprising an I-SceI site which encompasses the subject matter of claims 23, 24, 27 and 28 of instant application. Claim 18 ('732) is drawn to recombinant mouse or cultured cells comprising I-SceI site which encompass the subject matter of claim 39 of instant application. Claim 21 ('732) is drawn to a method, providing cells containing I-SceI site, and adding I-SceI endonuclease and transfecting a gene of interest which encompasses the subject matter of claim 31-32 of instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 23-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, **had possession of the claimed invention**, and as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **make and/or use** the invention.

Claims are drawn to a transgenic mouse and recombinant cells comprising a nucleotide sequence encoding I-Scel, wherein the pRSV Iscel or pCMV l-Scel is a plasmid. Claims are further drawn to the claimed transgenic mice wherein the I-Scel site has been introduced by retroviral infection selected from a group of vectors (as claimed). Claims are also drawn to a method of generating transgenic cells wherein cells from a transgenic animal (with one I-Scel site) are provided with I-Scel endonuclease to insert a gene of interest and a DNA sequence homologous to the sequence of chromosomal DNA, allowing homologous recombination. Claims are further drawn to a method where in the I-Scel site has been introduced via homologous or non-homologous recombination by performing viral infection or transfection (as claimed). Claims are further drawn to culturing transgenic cells from a transgenic animal. Claims are also drawn to a method of culturing transgenic cells from a transgenic mouse. In addition, claims are also drawn to a method of activation of a specific gene in a transgenic cell from a mouse by inserting I-Scel site into coding sequence of a gene, wherein the gene is activated by providing I-Scel endonuclease to the cell.

Claim 23-47 recites subject matter which is not described in the specification. Applicant is required to cancel the **new matter** in the reply to this Office action. Claim 23-30 are drawn to a transgenic mouse, wherein nucelotide sequences encoding I-SceI or having I-SceI site are either fed

or injected into a transgenic mouse, whereas the specification only describes a method of transfecting a mouse cell line, yeast cells or generic transgenic animals where genotype is altered by I-SceI coding sequence or an I-SceI site. Claims 31-45 are to method of generating and culturing transgenic cells from a transgenic animal, the specification provide no description of making transgenic cells by culturing from transgenic animals. Similarly the specification does not describe the transgenic mouse cells required for the method of claim 46-47. The specification only disclosed transgenic mouse cell lines but not the claimed method. Furthermore, the specification provide no support that applicants are in the possession of claimed invention.

Applicant is referred to the Interim guidelines on ***Written Description*** published June 15, 1998 in the Federal Register, Vol. 63, No. 114, pp. 32639-32645 (also available at www.uspto.gov). In analyzing whether the written description requirement is met for the claimed invention, it is first determined whether a representative number of species have been described by their complete structure (it is not realistic to expect that the "complete structure" of an animal, or even a cell, could be described. Therefore, the inquiry required by this portion of the written description guidelines is interpreted to be whether the phenotypic consequences of altering the genotype have been described).

In this case, the few disclosed embodiments are not representative of the products claimed. The claims encompass a transgenic mouse and recombinant cells provided from the transgenic mouse, comprising a nucleotide sequence encoding I-Scel. The transgenic animals encompass a huge genera of animals including insects, reptiles, birds and mammals encompassing mice, rabbits, sheep, pigs, cows and various primates. Next, it is then determined whether a representative number of species have been sufficiently described. The specification disclosed only a transgenic yeast or transformed/transfected mouse cells and fails to described even the claimed transgenic mouse (as claimed). The specification fails to describe the claimed products because transgenic yeast cells or transformed mouse cell lines are not predictive of is not predictive in any and all transgenic animals

including the transgenic mouse (as claimed). The limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that applicants were in possession of a transgenic mouse and recombinant cells (provided by the transgenic animal) as recited in the claims at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed invention.

Claims 23-47 are rejected because specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **make and/or use the invention.**

The instant specification also fails to provide enablement to one skilled in the art, to make and/or use the claimed invention. The specification teaches genetic recombination, especially the homologous recombination in the making of transgenic yeast (page 3, para.1-2, example 1, 2 and 3). The specification also teaches the making of virus producing ψ-2 packaging cell lines (page 64, para.2). The specification further teaches homologous recombination in mouse NIH3T3 fibroblast and mouse PCC7-s multipotent cell line using viral vectors (page 64, para.3, page 67, table-1). In addition the specification also teaches the use of I-SceI meganuclease to introduce double strand break mediated recombination in mouse 3T3 fibroblast cells using retroviral vectors (page 71, example-5, page 75, table-1, page 77, table-2). The specification only provide guidance to make recombinant mouse cells and yeast cells and base upon these results the specification further speculated that "the method can also be used with transgenic animals" (page 85 para.1, para.3). However, the specification fails to teach one skilled in the art, to make and/or use the claimed invention. The specification fails to provide guidance to any and all transgenic mouse or an animal comprising a nucelotide sequence encoding I-Scel introduced by homologous or non-homologous recombination. In addition, the specification also fails to provide guidance any and all recombinant cells provided by any and all transgenic animals.

The state of art at the time of filing teaches that transgene expression and the physiological results of such expression in transgenic animals was not always accurately predictable. It is well known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic animal are greatly dependent upon the specific expression vector used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, are the important factors that govern the expression of a transgene (Well RJ, Theriogenology 45:57-68, 1996; see page 61, para.2). Furthermore, many biochemical pathways are plastic in nature which reflects the ability of the embryo to use alternative gene when the preferred gene is modified (Kappel et al. Current Opinion in Biotechnology 3:358-353 1992, page 550, col.1, para. 3-4). In addition, genetic modulation via homologous recombination is highly unpredictable art which requires numerous step that often fails (Viville, in Transgenic Animals, Houdebine (eds), Harwood academic publishers, France. pp307-321, 1997). Embryonic stem (ES) cells are very sensitive to culture conditions and have natural tendency to differentiate, giving rise to unstable genome which render these cells unusable. Furthermore, homologous recombination remains a rare event and the injection of ES in the blastocyte is also unpredictable (Viville page 308). The specification only exemplified the retroviral infection of a mouse PCC7-s multipotent cell line using viral vectors but fails to show that implantation of any selected clone lead to the making of a trasgenic mouse or any and all animals (page 64, para.3, page 67, table-1). It is not clear how a mouse multipotent cell line would results in the development of the any and all species of the transgenic animals (as claimed). Furthermore, methods of claims 31-47 are not enabled because the method (as claimed) requires the use of cells obtained from a transgenic animal or a transgenic mouse. In addition, for the reasons set forth above the making of transgenic yeast or transfection of mouse cells in vitro does not recapitulate the complexities involved in the making of any and all transgenic animals. Although, one skilled in the art would have been able to make the claimed genetic constructs, it would have required excessive and undue experimentation to make a

transgenic mice or any and all transgenic animals, without a predictable degree of success because the specification only provide guidance to make a transgenic yeast.

Furthermore, as set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brian Stanton Ph.D. can be reached on (703) 308-2801. The fax phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

Sumesh Kaushal
Art Group 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER